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Gentamicin for Treatment of Neonatal Sepsis

A Landscape of Formulation,
Packaging, and Delivery Alternatives

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Acronyms

AFRINEST	African Neonatal Sepsis Trial
BFS	Blow-fill-seal
COGS	Cost of goods sold
DPI	Dry powder inhalers
DSJI	Disposable-syringe jet injector
ID	Intradermal
IM	Intramuscular
IV	Intravenous
LMICs	Low- and middle-income countries
MDI	Metered-dose inhalers
RUP	Reuse prevention
SIP	Sharps-injury prevention
SC	Subcutaneous
UNICEF	United Nations Children’s Fund
USAID	United States Agency for International Development
US FDA	United States Food and Drug Administration
WHO	World Health Organization

Executive summary

Neonatal infections are a significant cause of newborn mortality in low-resource settings. Treatment guidelines for neonatal sepsis recommend inpatient courses of intravenous or intramuscular antibiotics, but many infants do not receive such treatment because they lack access to facility-based care. Recently issued World Health Organization (WHO) neonatal sepsis guidelines expand treatment to the outpatient setting when referral is not possible or accepted.¹ Delivery of gentamicin in an outpatient setting will expand access to lifesaving medications for neonatal sepsis and potentially reduce the rate of infant mortality due to infection in the first days of life. However, current presentations require that providers be trained in dose calculation based on infant weight and have access to safe injection supplies and sharps disposal. An easy-to-use, less-invasive, affordable delivery method for gentamicin paired with an oral amoxicillin product has the potential to expand access to lifesaving outpatient antibiotic treatment for infants with severe infection during the neonatal period.

We conducted a landscape analysis to review the range of drug formulation, packaging, and delivery technologies that might be applied to gentamicin delivery for infants. The priority was to review technologies that could improve the safety and ease of delivery, reduce training requirements and the possibility of health care worker error, and expand access by potentially being suitable for use in a primary care setting. This report expands upon and updates a previous PATH HealthTech landscape of gentamicin delivery alternatives completed for the United States Agency for International Development (USAID) in 2010 (PATH, unpublished data, 2010). In the current report, we included alternative primary packaging and delivery devices for intramuscular injection as well as alternative formulations for different routes of delivery, such as oral, sublingual, pulmonary, rectal, and transdermal delivery.

Potential delivery technologies were compared based on parameters such as technical feasibility, usability, safety, cost, drug manufacturer requirements, and program logistics. Technologies that may be available in the near term include syringes printed with markings specifically for gentamicin doses. Medium-term options include fixed-dose blow-fill-seal ampoules for delivery with a reuse prevention needle and syringe, and prefilled delivery devices such as the Uniject® device.* Long-term development work would be needed for other promising delivery routes, such as oral liquids or dispersible tablets, intranasal drops, a rectal suppository or gel, and transdermal hydrogel microneedle patches.

The next steps to advance promising technologies to simplify gentamicin delivery in the short-term would be to conduct field-testing to assess the value of introducing custom syringes for this application. In parallel, it would be important to initiate market evaluations and engage pharmaceutical manufacturers to determine interest and viability of prefilled or fixed-dose presentation for intramuscular delivery. Technical feasibility studies of novel formulations for oral, intranasal, rectal, or microneedle patch delivery would be necessary.

* Uniject is a registered trademark of BD.

1 Background

Neonatal infections, including sepsis, comprise an estimated 26% to 36% of the neonatal deaths that occur globally in low- to middle-income countries.^{2,3} Approximately 400,000 newborns die each year from sepsis primarily in low-resource settings.⁴ Current World Health Organization (WHO) guidelines for treatment of neonatal sepsis of unknown etiology include hospitalization and 7 to 10 days of penicillin (or ampicillin) and gentamicin delivered intravenously or by intramuscular (IM) injection.⁵ The current parenteral treatment course requires trained health care workers to reconstitute the penicillin (or ampicillin), calculate the correct antibiotic dose and delivery schedule for both penicillin (or ampicillin) and gentamicin based on the infant's weight, draw up the specified quantities accordingly, and deliver the drugs with a needle and syringe in the correct injection site, or by intravenous (IV) infusion. The complex treatment scheme has prevented treatment in community-based or outpatient settings. Based on recent clinical trials conducted in Africa and Asia,^{6,7,8} WHO has issued new guidelines for outpatient treatment of neonatal sepsis when referral is not possible or accepted.¹ These new regimens include IM gentamicin and oral amoxicillin, which are described in more detail in section 1.2. Alternative formulation, packaging, and delivery options are potentially applicable for gentamicin delivery, including fixed-dose presentations for needle and syringe injection, prefilled delivery devices, and formulations for alternative routes of delivery. Each of these approaches has varying advantages in terms of cost, ease of use, and safety, which are reviewed in the landscape analysis that follows.

1.1 Current formulation and presentation

Gentamicin for injection is presented as an aqueous solution of gentamicin sulfate. Gentamicin is also available in eye drops for ophthalmological infections, in ear drops for ear infections, and as a topical ointment for skin infections. For the injectable route of delivery, gentamicin is mostly available in 2 ml ampoules or vials in two concentrations (10 mg/ml or 40 mg/ml), but other concentrations and vial/ampoule sizes are available from some manufacturers. Both the 10 mg/ml and 40 mg/ml concentrations are produced in a multi-dose 2 ml vial/ampoule format containing preservatives, and the 10 mg/ml concentration is also available as a single-dose 2 ml vial/ampoule format without preservatives. WHO previously recommended using 10 mg/ml presentations or diluting 40 mg/ml vials with sterile water to 10 mg/ml prior to drawing infant doses for IM injection.⁵ WHO implementation recommendations for the new guidelines are currently in development and are expected to allow doses to be drawn from undiluted 40 mg/ml presentations.

Gentamicin sulfate is a highly polar, water soluble (> 50 mg/ml), hydrophilic drug with extremely low lipid solubility and low partition coefficient.[†] The drug formulation includes water for injection, methylparaben and propylparaben as preservatives, sodium metabisulfite, and edetate disodium. The

[†] It is a mixture of three major components (free base) in the ratio C1 (MW: 477.6): < 45% C1a (MW: 449.5): < 35% C2 (MW: 463.6) < 30%.

WHO Model List of Essential Medicines recommends a vial presentation for gentamicin, but many developing-country suppliers sell it packaged in glass ampoules.^{9,10,11} For typical neonatal dosages, approximately two doses could be obtained from a 10 mg/ml vial and up to eight doses from a 40 mg/ml vial. For ampoules, any drug not immediately used would have to be discarded as it could not be resealed. Gentamicin is stable stored at 2°C to 30°C, but some product labels require controlled room-temperature storage (20°C to 25°C).¹²

1.2 Treatment regimens

For treatment of neonatal sepsis, gentamicin is delivered IV or by IM injection. The dosage of gentamicin is calculated based on patient weight to ensure the appropriate serum concentrations are obtained for safety and efficacy of the drug. Gentamicin has a narrow treatment window and incorrect usage can cause toxicity to the ears, kidneys, and neurological system. The recommended dose range for treatment of neonates is a total of 3 to 7.5 mg/kg/day, with one to three doses per day for seven to ten days.^{5,13} The WHO-recommended weight bands of gentamicin for inpatient treatment are summarized in Table 1. Updated WHO recommendations on gentamicin weight bands for outpatient treatment are in development but are not yet available.

Table 1. WHO-recommended gentamicin weight bands for inpatient treatment of neonatal sepsis.¹⁴ (All doses to be drawn from a 10 mg/ml stock concentration).

Infant weight	Low birth weight, 1 st week of life (3 mg/kg IM or IV once daily)	Normal birth weight, 1 st week of life (5 mg/kg IM or IV once daily)	Weeks 2-4 of life (7.5 mg/kg IM or IV once daily)
1≤1.5 kg	0.3–0.5 ml		0.75–1.1 ml
1.5≤2 kg	0.5–0.6 ml		1.1–1.5 ml
2≤2.5 kg	0.6–0.75 ml		1.5–1.8 ml
2.5≤3 kg		1.25–1.5 ml	1.8–2.2 ml
3≤3.5kg		1.5–1.75 ml	2.2–2.6 ml
3.5≤4 kg		1.75–2.0 ml	2.6–3.0 ml
4≤4.5kg		2.0–2.25 ml	3.0–3.3 ml

Many infants with potential sepsis do not receive treatment because they do not have access to hospitals or facility-based care; in response, community-based models for identification and treatment of neonatal infections have been developed.¹⁵ More recently, simplified treatment regimens have been tested for outpatient treatment of neonatal sepsis, including IM injection of gentamicin along with an oral antibiotic, and studies indicate that this approach can be safe and effective.^{6,7,8,16,17,18} A simplified course could

enable outpatient treatment and allow alternatives to conventional packaging and delivery methods, potentially enabling delivery by community health workers to expand access.¹⁶

Extended-interval dosing of gentamicin using three infant weight categories requires only two different dosages of gentamicin to treat the full range of newborn sizes.¹⁶ This approach reduces the burden of dose calculation on health care providers and could enable easy-to-use, fixed-dose presentations, such as Uniject.¹⁹ Details of this dosing schedule are provided in Table 2.

Table 2. Extended-interval dosing of gentamicin for treatment of neonatal sepsis.¹⁶

Infant weight	Gentamicin dose	Dose volume (10 mg/ml concentration)	Dose volume (40 mg/ml concentration)	Schedule	Total doses/treatment course
< 2 kg	10 mg	1.00 ml	0.25 ml	Every 48 hours	5
2–2.5 kg	10 mg	1.00 ml	0.25 ml	Every 24 hours	10
≥ 2.5 kg	13.5 mg	1.35 ml	0.34 ml	Every 24 hours	10

Recent clinical trials compared the efficacy of simplified treatment regimens including shorter courses of injectable antibiotics. The African Neonatal Sepsis Trial (AFRINEST) group conducted a trial in the Democratic Republic of the Congo, Nigeria, and Kenya to compare alternative treatment regimens for newborns exhibiting symptoms of neonatal sepsis.⁷ The study included the following treatment arms, each provided in an outpatient setting:

- Injectable procaine benzylpenicillin and gentamicin for 7 days
- Injectable gentamicin and oral amoxicillin for 7 days
- Injectable procaine benzylpenicillin and gentamicin for 2 days, then oral amoxicillin for 5 days
- Injectable gentamicin for 2 days and oral amoxicillin for 7 days

A similar trial in Bangladesh compared the following:

- Injectable procaine benzylpenicillin and gentamicin for 7 days
- Injectable gentamicin and oral amoxicillin for 7 days
- Injectable procaine benzylpenicillin and gentamicin for 2 days, then oral amoxicillin for 5 days

Both studies found that the alternative regimens containing fewer doses of intramuscular antibiotics were similarly efficacious as the standard treatment guidelines.⁸ The Bangladesh study used a system of 13 weight bands, each with a different gentamicin dose, shown in Table 3.²⁰ The number of weight bands in the dosing regimen for the AFRINEST study was not specified in publications, but the trial included weight-based calculation of doses, providing 4 mg/kg to neonates in the first week of life and 7.5 mg/kg to older newborns.^{7,21}

Table 3. Gentamicin dosage for each of 13 weight bands used in Bangladesh study of alternative treatment regimens for neonatal sepsis.²⁰

Infant weight	Gentamicin dose	Volume of dose from 40 mg/ml stock concentration
1.500–1.749 kg	7.20 mg	0.18 ml
1.750–1.999 kg	8.00 mg	0.20 ml
2.000–2.499 kg	10.00 mg	0.25 ml
2.500–2.999 kg	12.00 mg	0.30 ml
3.000–3.499 kg	14.00 mg	0.35 ml
3.500–3.999 kg	16.00 mg	0.40 ml
4.000–4.499 kg	18.00 mg	0.45 ml
4.500–4.999 kg	20.00 mg	0.50 ml
5.000–5.499 kg	22.00 mg	0.55 ml
5.500–5.999 kg	24.00 mg	0.60 ml
6.000–6.499 kg	26.00 mg	0.65 ml

Based on these study results, new guidelines for the outpatient treatment of neonatal sepsis when referral is not possible or accepted have been determined by a group of experts led by the WHO.¹ Simplified weight bands and corresponding dosages for gentamicin are being determined by WHO, and it is anticipated that three weight bands will be likely recommended. Countries adopting the new outpatient treatment guidelines might choose different weight bands. The number of weight bands will impact the feasibility of some alternative packaging and delivery options for injectable gentamicin. For the prefilled and fixed-dose potential presentations of gentamicin described in this landscape analysis, multiple versions containing different dosages would have to be manufactured, purchased, distributed, and stored, and users would need to be trained to identify the appropriate dose for each patient.

1.3 Costs and manufacturers

Gentamicin is a generic drug that is produced by multiple manufacturers in both developed and developing countries (Table 4). Gentamicin is relatively inexpensive. The price of gentamicin for injection is typically around US\$0.05 for a 2 ml, 10 mg/ml presentation.^{22,23} Prices vary according to volume of purchase and presentation of the drug.

Table 4. Selected manufacturers of gentamicin.²²

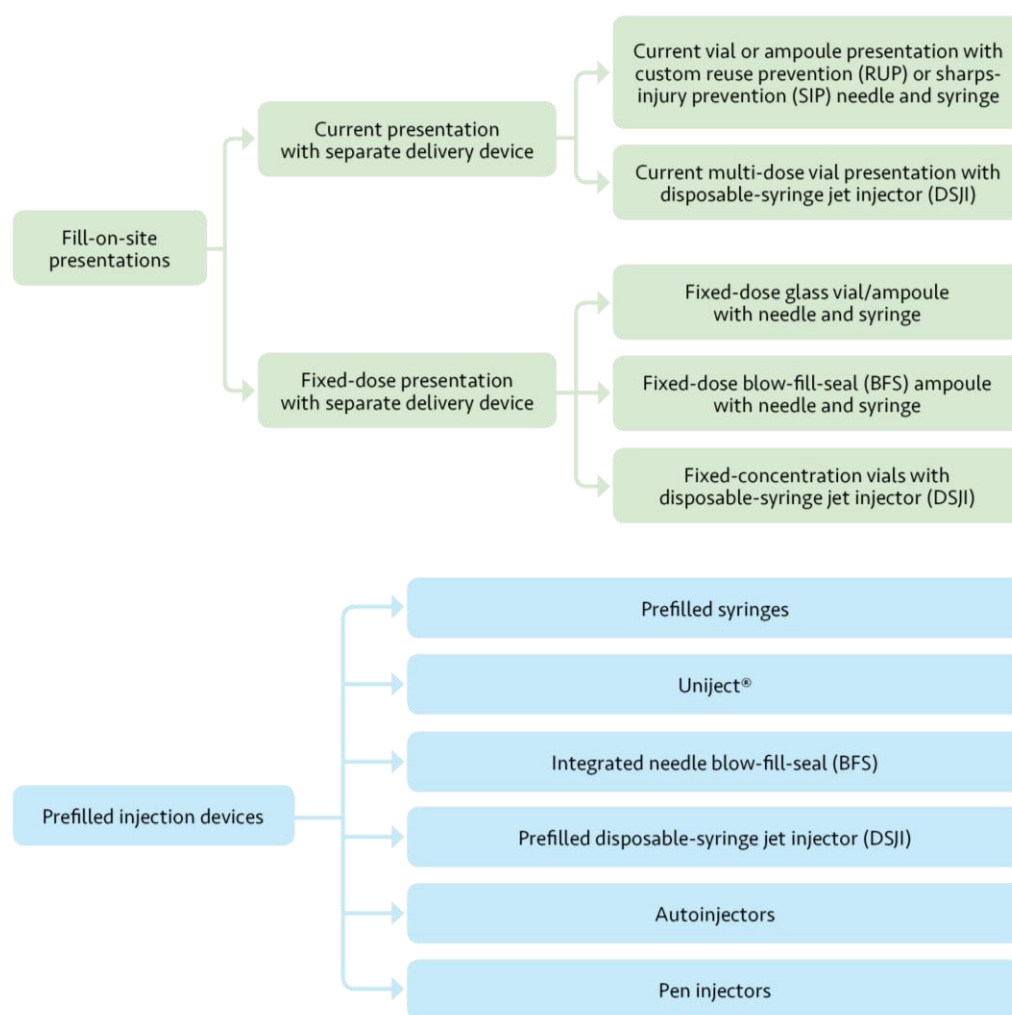
Manufacturer	Country	Presentation	
		40 mg/ml in 2 ml vial	10 mg/ml in 2 ml vial or ampoule
Alpha Laboratories Ltd	India	Y	
Apex	India	Y	
BDH	India	Y	
Esco	India	Y	Y
Fulford India Ltd	India	Y	
Guilin	China	Y	
Hospira	United Kingdom	Y	
Incepta	Bangladesh	Y	Y
Medochemie	Cyprus	Y	
Neon	India	Y	
Panpharma	France	Y	Y
Pharmatex	Italy	Y	Y
Piramal	India	Y	
Sandoz	Germany	Y	
Sanjivini Parenteral	India	Y	
Strides	India	Y	

2 Packaging and delivery devices for intramuscular injection of gentamicin

Packaging and delivery device options for IM delivery of a liquid drug fall into two main classes: fill-on-site presentation or prefilled presentation. For delivery devices intended to be filled on site from a separate primary container, currently available gentamicin vials or ampoules could be used, or new, fixed-dose presentations could be developed. For needle and syringe delivery, we focused on devices that are available with reuse prevention and needlestick-prevention features.[‡] Needle-free IM delivery devices, such as disposable-syringe jet injectors, were also included in the landscape analysis. The various packaging and delivery technologies reviewed are summarized in Figure 1.

[‡] The term autodisable (AD) is typically used for immunization syringes. For curative syringes, reuse prevention (RUP) is the preferred term and incorporates syringes with either automatic or elective disabling features.

Figure 1. Classification of intramuscular packaging and delivery devices. .



Fill-on-site presentations

2.1.1 Current presentation with separate delivery device

2.1.1.1 Current vial or ampoule presentation with custom RUP or SIP needle and syringe

Technology description: A potentially simple solution to allow community-based therapy is to use current gentamicin vials and distribute customized syringes for delivery of appropriate doses of gentamicin for the various weight bands of neonates. The dose volumes for gentamicin treatment could be marked by color or symbols, thereby reducing potential errors and simplifying use by lesser-trained health workers. This could entail customized printing on the syringe itself or application of a label onto existing syringes. Delivery devices with custom-marked dose volumes are currently co-packaged with several over-the-counter and veterinary medications. Examples include oral syringes packaged with infant Advil and oral

syringes provided with several manufacturers of meloxicam, a prescription nonsteroidal anti-inflammatory drug used for treatment of pain and inflammation in companion animals (Figure 2).

Figure 2. Custom-printed oral syringes marketed for dosing with infant Advil (marked with doses in ml for treatment of infants of different weights) and veterinary Loxicom (marked with image denoting species and dose volumes per the animal's weight in kg).



Photos: Pfizer, Norbrook Laboratories

Implications for expanding access: Currently available gentamicin presentations require the health care worker to draw up the appropriate dose volume using the measurement scale on a syringe. Community health workers or midwives who may be targeted by certain country governments for providing treatment of neonatal sepsis may not be trained to deliver medicine by needle and syringe; lack of training may preclude this approach. Due to the multiple calculations needed to determine the dose volume by age and weight of the newborn, health workers at the primary care level may also have difficulty accurately measuring the correct amount of drug they should administer. Syringes with custom dose markings for the specified neonatal doses of gentamicin could simplify the process of preparing gentamicin injections for busy health workers and reduce the risk of drawing an improper dose. This approach has the advantage of not requiring any repackaging or relicensing of the drug product and could be a very low-cost solution. It would be essential to ensure that health care workers using the syringe have access to the appropriate concentration of gentamicin to ensure the correct dose is drawn. Custom dose markings would lessen, but not eliminate, the risk of re-purposing syringes provided for gentamicin delivery for injection of other medications. Curative syringes with reuse prevention (RUP) features are priced between US\$0.042 and US\$0.078, which is slightly higher than the cost of standard non-RUP syringes (estimated at US\$0.01 to US\$0.04), but would help ensure that syringes are not reused.²⁴ Use of a syringe with sharps-injury prevention (SIP) features, such as a retractable needle or needle shield, would have additional safety benefits for prevention of needlestick injuries and safer disposal. WHO-prequalified SIP syringes cost US\$0.095 each. See Figure 3 for examples of RUP and SIP syringes.

Figure 3. Examples of A) a reuse-prevention syringe (SoloMed from BD with breakable plunger) and B) a sharps-injury prevention syringe (SecureGard from SafeGard Medical, pre- and post-retraction of needle) for curative use.



Photos: PATH/Patrick McKem

2.1.1.2 Current multi-dose vial presentation with disposable-syringe jet injector

Technology description: Disposable-syringe jet injectors (DSJIs) are a needle-free injection technology system that can deliver injections intramuscularly (IM), subcutaneously (SC), or intradermally (ID), depending on the device. DSJIs use a sterile, disposable needle-free syringe for each injection and can be filled from conventional vials using filling adapters. A reusable injector powered by a spring or compressed gas provides the force that enables the injection to penetrate through the skin using a high pressure liquid stream. Some DSJIs utilize needle-free syringes with variable dose markings, enabling users to measure the required dose from an existing gentamicin vial. Example of DSJI devices in this category are the Bioject® Biojector® 2000 (gas powered) and ZetaJet™ (spring powered) devices. The ZetaJet™ has United States Food and Drug Administration (US FDA) and CE mark clearance and is commercially available, but it does not have WHO prequalification (Figure 4). One jet injector model does have WHO prequalification (PharmaJet Stratis®), but it is a fixed-dose device (see section 2.1.2.3 for a description of the potential use of fixed-dose DSJIs for gentamicin delivery).

Implications for expanding access: Since jet injectors do not use a needle for injection, they provide an advantage in safety and eliminate the need for sharps waste disposal systems. Some DSJIs are capable of delivering variable doses of drugs and could be used to deliver IM doses of gentamicin from existing vial presentations. Due to the maximum dose volume of marketed variable-dose DSJIs (0.5 ml for the ZetaJet™, 1 ml for the Biojector2000), an undiluted 40 mg/ml gentamicin presentation would likely have to be used. The amount of training required to learn to correctly draw doses and use a field-filled DSJI and the time needed to prepare and deliver the injection would be similar to that needed to learn to draw and deliver an injection with a standard needle and syringe. The reusable device component would have to be stored by the health worker between patients. WHO-prequalified DSJIs are validated for use for a minimum of 20,000 injections, making the cost of the reusable device (estimated at US\$100 to US\$200) very low if it can be spread over many injections. The disposable components of the system (needle-free syringe and vial adapter) could potentially cost a total of US\$0.50 per injection at high volumes. In a primary health care setting, an individual clinic is expected to treat few suspected sepsis cases, so the

reusable device cost would likely be prohibitive, unless the same device could be used for other applications such as vaccination.

Figure 4. Bioject® ZetaJet™ variable-dose DSJI.



Photo: Bioject

2.1.2 Fixed-dose presentation with separate delivery device

2.1.2.1 Fixed-dose glass vial/ampoule with needle and syringe

Technology description: An alternative to further simplify gentamicin delivery would be to package gentamicin in premeasured, single-dose vials or ampoules. The drug label could be color coded to differentiate between the dosages for varying infant weights. Health care workers could be trained to draw up the entire dose and deliver the injection using a standard single-use syringe with safety features.

Implications for expanding access: This approach would make it easier for health workers in a primary health care setting to determine and draw the correct dose of gentamicin. In some countries, community health workers and midwives may not be authorized to give injections with a needle and syringe due to the perceived risk of them delivering other drugs without proper training or equipment, which could preclude this option if broader delivery scenarios are envisioned. The use of a fixed-dose presentation with a needle and syringe could, however, be an inexpensive option, as 20-mg ampoules of gentamicin are currently on the market for as low as US\$0.05, and RUP syringes cost around US\$0.04. However, prices for fixed-dose presentations might not be as low as these estimates due to lower purchasing volumes of gentamicin in this format as well as additional costs to manufacturers for relicensing and production start-up. The feasibility of a fixed-dose presentation also depends on the number of recommended weight bands, as producing, distributing, and stocking multiple presentations will add some complexity. For additional safety to prevent needlestick injuries and reduce hazards if sharps waste disposal is inadequate, a SIP syringe could be used instead for an increased cost of approximately US\$0.10 per injection.

2.1.2.2 *Fixed-dose blow-fill-seal ampoule with needle and syringe*

Technology description: Fixed-dose plastic blow-fill-seal (BFS) ampoules are plastic containers generally made from polyethylene or polypropylene that are extruded, blown, filled, and sealed in an automated, continuous process under sterile conditions. Since BFS ampoules are composed of plastic, they can be more robust than glass and difficult to break, making secondary packaging and transportation easier. They also eliminate the health worker's risk of laceration, which can occur with traditional glass ampoules, as well as the risk of glass particulates being injected into the patient.²⁵ To use a standard BFS ampoule for parenteral injection, the user separates an ampoule from the strip, shakes down any contents from the neck, twists the top open, and connects a luer-tip syringe directly onto the ampoule to draw the pharmaceutical for delivery. Alternatively, a syringe with a needle can be used to draw from the ampoule.

BFS containers are used widely as a primary packaging technology for pharmaceutical applications, as well as for food and cosmetic products. Of the global market of approximately 5 billion containers annually, about half (2.5 billion containers) are inhalation vials, 2 billion are ophthalmic vials, and 500 million are for other purposes (aqueous solutions and small-volume products such as local anesthetics and diluents). BFS packaging has also been studied for vaccines, including live attenuated influenza vaccine and rotavirus vaccine.²⁶ Gentamicin eye drops are currently manufactured in a BFS bottle by Vitaline, a Peruvian BFS contract manufacturer, and sold in Costa Rica and Bolivia (Figure 5A).²⁷ Gentamicin for injection is produced in an 80 mg, 2 ml BFS ampoule by Pfizer (Figure 5B). This presentation is currently manufactured in Pfizer's Perth, Australia, BFS facility and marketed in Australia, New Zealand, and Singapore.

Implications for expanding access: BFS ampoules have advantages for transport, storage, disposal, and safety, as there is no danger of broken glass, and ampoules can be designed to allow filling of syringes without needles. However, BFS requires high start-up costs for the filling line technology if it is not available at the drug manufacturer; alternatively, it could be filled by a BFS contract manufacturer. Drugs for packaging in BFS must be tested for stability through the changes in temperature involved in the packaging process and tested for compatibility with the specific polymer formulations. Gentamicin appears to be compatible with the BFS fill/finish packaging process, given the current availability of gentamicin products in this presentation on the market. Based on a cost of goods sold (COGS) analysis conducted by PATH for packaging rotavirus vaccine, at high production volumes, packaging single-dose drugs in BFS ampoules is expected to be less expensive than glass vials. It could potentially be similar in cost to glass ampoules. BFS packaging becomes less cost-effective at lower production volumes.

Figure 5. A) Gentamicin in blow-fill-seal (BFS) bottle for eye drops and B) gentamicin in BFS ampoules for injection.



Photos: A) Vitaline, B) Pfizer

A

B

2.1.2.3 Fixed-concentration vials with disposable-syringe jet injector

Technology description: In addition to the variable-dose DSJIs described previously, DSJI devices have also been developed to deliver fixed-dose volumes, as vaccines are typically delivered in 0.5 ml doses. One such device is the Stratis® manufactured by PharmaJet (Figure 6), which is designed to be suitable for use in developing-country settings and can deliver SC and IM injections for all ages. The Stratis® device has clearance from the US FDA and several other national regulatory authorities, as well as WHO prequalification. It is currently marketed in the United States for delivery of bioCSL's Afluria influenza vaccine. The Stratis® device has been used in a pilot measles vaccine campaign in Cambodia and has been evaluated in clinical trials in low- and middle-income countries (LMICs), including inactivated poliovirus (IPV) vaccine delivery in the Gambia and measles-mumps-rubella and pentavalent vaccine delivery in India. For needle-free IM delivery of gentamicin, the Stratis® device could be paired with a series of fixed-dose gentamicin vials containing the recommended dosages of gentamicin for newborns formulated in concentrations such that each dose is 0.5 ml.

Implications for expanding access: Fixed-concentration gentamicin vials used with a fixed-dose DSJI would eliminate sharps and reduce the possibility of a filling error. Use of these devices with gentamicin would require that the drug be reformulated into the appropriate concentrations to provide the correct doses in a 0.5 ml fixed-dose syringe. Similar to the variable-dose DSJIs reviewed earlier in this report, training requirements and time required for delivery would be similar to needle and syringe injections. As described previously, as the number of patients needing sepsis treatment in a primary health care setting is anticipated to be low, the reusable device would not be used frequently, and the amortized cost per dose of the reusable and disposable DSJI components would likely be too high for use for this application.

Figure 6. PharmaJet Stratis® fixed-dose disposable-syringe jet injector (DSJI) for subcutaneous (SC) and intramuscular (IM) delivery.



2.2 Prefilled injection devices

2.2.1 Prefilled syringes

Technology description: To simplify treatment, prefilled syringes could be produced containing the various standard dosages of gentamicin. Prefilled syringes are filled by the pharmaceutical manufacturer and delivered to the health care system, serving as both the primary drug container and the delivery device. They reduce the number of steps required to deliver an injection—making the process easier and faster for the user—and reduce the potential for dosing errors. Often prefilled syringes are made of glass, which have a greater risk of breakage during storage. Syringes made of plastics, such as cyclic olefin copolymer and cyclic olefin polymer, have recently been introduced; these materials provide greater flexibility in design but are also more expensive than glass syringes (Figure 7A).²⁸ WHO prequalification requires that prefilled injectable vaccines have an auto-disable feature to prevent syringe reuse.²⁹ Standard glass and polymer prefilled syringes do not have features to prevent reuse or needlestick injuries. Needlestick-prevention features that automatically shield the needle after injection are available and can be either integrated with the prefilled syringe system itself, as in the Unifill® safety syringe, manufactured by Unilife Medical Solutions, or manufactured separately and provided as an additional option to the prefilled syringe. Examples of auxiliary safety fixtures include the min-Max® passive safety device manufactured by tip-top, the UltraSafe passive delivery system manufactured by Safety Syringes, and the Companion Guide-On™ needle cover manufactured by Credence MedSystems (Figure 7B).^{30,31,32} These passive needle guards are designed to be compatible with standard prefilled syringes. Other examples of clip-on safety mechanisms for prefilled syringes include the BD Preventis, the West Clip'n'Ject, and the Specialized Health Products International LuproLoc.

Implications for expanding access: Prefilled injection devices eliminate the need to draw up or measure medications, which improves speed, ease of delivery, and dosing accuracy³³ (important considering the potential toxicity of incorrect doses of gentamicin). Use of prefilled syringes for delivery of vaccines and parenteral drugs is rapidly increasing in developed countries due to recognition of the advantages they

give in safety, correct dosing, and ease of preparation and use.³⁴ However, prefilled syringes are significantly more costly to manufacture than non-prefilled presentations. The primary cost driver for prefilled syringes as compared to glass vials is the primary container. The cost to the pharmaceutical manufacturer of procuring ready-to-fill glass syringes can range from US\$0.40 to US\$0.60, in addition to the cost of the drug and fill/finish processing. Glass prefilled syringes are currently not recommended for vaccines in LMICs due to their bulky packaging and resulting large cold-chain storage volumes, as well as the difficulties they present in disposal, since they cannot be easily incinerated at typical clinic facilities.^{35,36}

Figure 7. A) Examples of Gerresheimer glass prefilled syringes with luer lock, luer cone, and staked needle. B) Credence MedSystems Companion Safety Syringe with needle exposed and retracted after injection.



Photos: PATH/Patrick McKern, Credence MedSystems, Inc.

2.2.2 Uniject

Technology description: The BD Uniject™ injection system is a compact, prefilled auto-disable delivery device that contains a small reservoir that is filled with drug or vaccine (Figure 8A). The Uniject injection system from BD has four main components: drug reservoir, port, needle assembly, and needle shield. The needle assembly consists of a hub and cannula (needle). The reservoir is a three-layer laminate film with linear low-density polyethylene as the fluid contact layer. The port and the valve (both in contact with the drug) are low-density polyethylene. The hub is polystyrene and the needle shield is polypropylene. Typically a foil-laminate pouch is utilized for filled Uniject units as the secondary package to maintain stability of the pharmaceutical. A needle-free version designed for oral delivery, the Uniject DP, is also available for market use (Figure 8B).

A standard prefilled syringe has a plunger that is pushed to expel the drug, whereas the Uniject system relies on the plastic reservoir (bubble) that is squeezed to dispense the drug. The Uniject design is available in four dose-volume sizes: 0.25, 0.5, 1.0, and 2.0 ml. It can be made available with standard needle gauges and lengths, ranging from 18 to 26 gauge and needle lengths of 3/8 to 1-1/2 inches. The

container is provided sterile in “ready-to-fill” reels for filling and heat sealing on a custom machine.³⁷ Uniject has been WHO-prequalified for vaccines and meets WHO requirements for an autodisable feature to prevent reuse.

Hepatitis B and tetanus toxoid vaccines made by BioFarma (Indonesia) and pentavalent Quinvaxem[®] vaccine made by Crucell (South Korea) have been WHO-prequalified in Uniject formats.³⁸ Sayana Press, a Uniject presentation of the contraceptive Depo-Provera, has also received approval and is currently being used in country-led pilot introduction studies in Bangladesh, Burkina Faso, Niger, Senegal, and Uganda.³⁹

Implications for expanding access: The Uniject was specifically designed to make injections safe and easy to deliver and to be used by health workers without previous experience using conventional syringes. A study evaluating gentamicin in Uniject in Nepal found that community health workers were able to safely treat infants with suspected infection in their homes and demonstrated that alternative delivery presentations of gentamicin were acceptable to health care workers and families.¹⁹ Use and acceptability studies in both Vietnam and rural Indonesia found that the majority of midwives interviewed preferred using the Uniject prefilled injection device compared to a standard ampoule or vial and syringe to deliver oxytocin during the third stage of active labor for management of postpartum hemorrhage.^{40,41} The midwives noted that the Uniject device enabled them to deliver the correct dose, with sterile injection equipment and proper disposal, in a safe and timely manner. The ease and convenience of the Uniject device could potentially reduce the amount of training required by health workers to administer a successful injection.

Because workers using Uniject would not be trained to use a standard syringe, they would lack the skill to give unauthorized injections of other drugs. The Uniject device is autodisable, but additional safety features such as needle shield or retractable needles are not available, and a sharps waste disposal system, such as a needle cutter, would be required for safe disposal of used devices. A 2010 cost analysis⁴² estimated the in-country price per dose to purchase gentamicin in Uniject to be US\$1.00 to US\$1.35, but these estimates will be reviewed and updated when WHO determines the new weight bands for outpatient treatment of neonatal sepsis.

Figure 8. A) BD Uniject and B) Uniject dispenser for oral delivery.



Photos: PATH/Patrick McKern

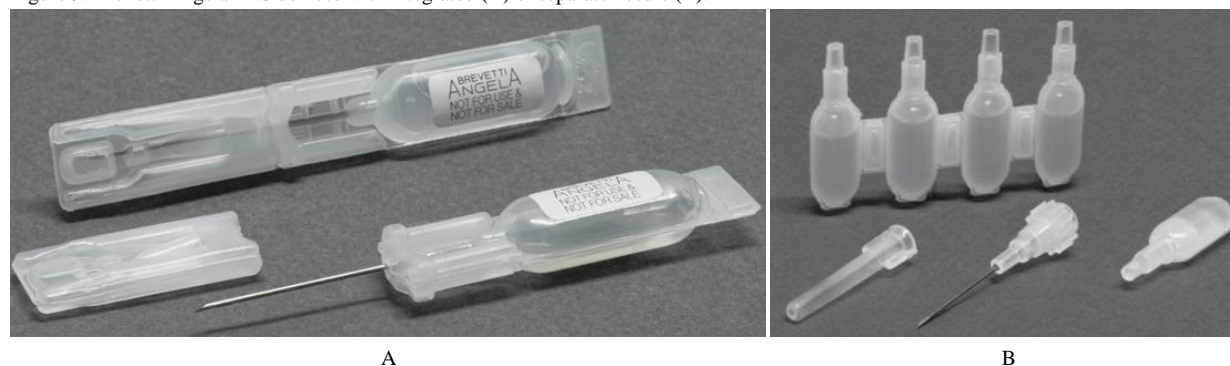
2.2.3 Integrated needle blow-fill-seal

Technology description: Brevetti Angela has developed the Syfpac® Secureject® BFS system in which a needle is integrated into the ampoule during forming, creating a prefilled syringe (Figure 9A).⁴³

Alternatively, a separate needle could be directly attached by the user to a BFS ampoule and used as a delivery device (Figure 9B). Previously rommelag® developed a design that incorporates a needle with a bellows BFS design, in which the needle is shrouded within the sealed closure of the BFS container and stays sterile until the cap is twisted off, and the company is developing a new integrated-needle BFS design.⁴⁴

Implications for expanding access: A BFS container designed to deliver a parenteral injection with integrated or separate needle could have similar advantages as Uniject in transportability and ease of use by health care workers in a variety of settings. Manufacturing costs for an integrated needle BFS container would be higher than a BFS ampoule designed for delivery with a separate needle and syringe due to the increased complexity of the design and the manufacturing process, but could still be low cost in comparison to traditional prefilled syringes, although this would depend on container design and manufacturing volume. Research assessing the functionality, usability, and suitability of integrated needle BFS designs for gentamicin would need to be conducted to assess the feasibility of this technology. Current designs may need to be optimized, as compact, prefilled auto-disable BFS delivery devices, are a technology in development. The cost of the device will depend on the scale-up manufacturing efficiency and volumes of production. Traditional BFS fill equipment is more efficient in the rate of units filled per minute and the footprint of the fill/finish equipment is more compact than filling equipment for glass vials or other compact, prefilled auto-disable delivery devices such as Uniject. Whether these advantages will extend to the manufacturing process for the new integrated needle design are yet to be determined.

Figure 9. Brevetti Angela BFS devices with integrated (A) or separate needle (B).



Photos: Brevetti Angela
www.brevettiangela.com

2.2.4 Prefilled disposable-syringe jet injector

Technology description: Some jet injectors can be prefilled. PharmaJet is developing a prefilled syringe option for the Stratis® jet injector delivery device (Figure 6), which will be made of medical grade polymer that meets stability requirements and leachable/extractable requirements for long-term storage of drugs and biologics. The US FDA has recently approved bioCSL's Afluria influenza vaccine for delivery with PharmaJet's fill-on-site Stratis® device,⁴⁵ and PharmaJet is investigating additional applications for a prefilled syringe system. Battelle manufactures a single-use, disposable jet injector called the DosePro® that propels a plunger forward through a prefilled glass cartridge to emit a small jet of fluid through the nozzle subcutaneously.⁴⁶ The first commercially available application of the DosePro® device was Sumavel® DosePro® for delivery of sumatriptan for migraines, which was approved and launched in the United States in 2010 and in Europe in 2011.⁴⁷ BioJect's Iject® device is designed to administer prefilled cartridges and the Jupiter Jet™ to administer prefilled syringes by ID, SC, or IM injection.^{48,49}

Implications for expanding access: Use of a prefilled, needle-free injection device would offer benefits in terms of safety and ease of use, as there would be no sharps waste or filling steps and the injection device could not be used to deliver other drugs. Like the other prefilled and fixed-dose gentamicin formats, multiple different prefilled presentations would be required to allow for different dose levels. Due to the technology's development status and the need for a relatively costly reusable jet injector delivery device, this option would have high start-up and continuing costs compared to other alternatives for IM delivery.

2.2.5 Autoinjectors

Technology description: Autoinjectors deliver a single dose of medication and are designed to make it easier for patients to self-administer an injection at home, and therefore these devices could also simplify delivery of injectable drugs by health workers in community settings. Autoinjectors typically encapsulate a glass or plastic prefilled syringe, shielding the needle from view before and after the injection (Figure 10). The devices are designed to not look like syringes and utilize springs to trigger needle insertion and injection by the press of a button. Upon pressing a button, the tip of the needle is exposed to penetrate the skin and the drug is automatically delivered via SC or IM injection, depending on the required injection depth. Once the injection is complete, most autoinjectors have a visible indication confirming the full dose was administered. Autoinjectors are manufactured by several companies—examples include the BD

Physioject™, West Confidose®, and Janssen SmartJet—and are used for injection of epinephrine, hormones, and drugs for rheumatoid arthritis and anemia. Autoinjectors for emergency use include the EpiPen®, which provides a dose of epinephrine as an antidote for life-threatening allergic reactions.⁵⁰

Implications for expanding access: Autoinjectors have been developed to further improve on the usability of prefilled syringes and to facilitate self-injection by patients and non-medical professionals. This technology has the potential to facilitate delivery of gentamicin by health workers with limited training. However, a single-use autoinjector is likely to be significantly more expensive than a prefilled syringe alone and may not be a viable alternative from a cost perspective.

Figure 10. Example of an autoinjector: ConfiDose from West Pharmaceuticals.



Photo: ConfiDose® is a registered trademark of Medimop Medical Projects Ltd., a subsidiary of West Pharmaceutical Services, Inc.

2.2.6 Pen injectors

Technology description: Pen injectors (also known as pens) are designed to hold 1.5 ml or 3 ml prefilled cartridges, from which multiple doses can be delivered until all the medication is used (Figure 11). The drug is delivered through a single-use disposable needle and the pen itself can either be disposable or reusable with replacement drug cartridges. The dose volume on an insulin pen is set by turning a dial and viewing an indicator window, and the injection is delivered by pressing a button. Pens are also used by patients for daily self-injections of hormones and other drugs. Pen injectors are designed to be easier to use than a standard syringe by non-medical professionals or people with mild disabilities and are manufactured by a number of different companies. Examples include products from BD (BD Vystra™ Disposable Pen and BD™ Reusable Pen), Ypsomed (Ypsomed UnoPen™ disposable pen for liquid pharmaceuticals and Ypsomed LyoTwist™ disposable pen for reconstitution, priming, and injection of lyophilized pharmaceuticals), and Owen Mumford (Autopen®). Examples of brand name insulin pens for diabetic patients include the Lantus® SoloSTAR®,⁵¹ the Novo Nordisk NovoLog® FlexPen®,⁵² and the Levemir® FlexTouch®. Other drugs available in pens include PegIntron from Merck, indicated for hepatitis C,⁵³ and APOKYN® (apomorphine) from Vetter Pharma-Fertigung GmbH & Co., indicated for motor symptoms of Parkinson's disease.⁵⁴

Another example of a cartridge-based delivery device is Duoject's VaccJect.⁵⁵ The device contains an integrated, automatic needle-disable system that retracts and locks the needle once an injection is administered. The needle is never exposed during the course of an injection. The pharmaceutical is contained in a standard cartridge that is inserted into the delivery device prior to delivery of the injection.

Implications for expanding access: Pen injectors are designed to be easier to use than a standard syringe and are used by health care workers as well as for self-injection by patients. Insulin is delivered SC, but an IM injection could be obtained by using the correct needle gauge and length. A redesigned pen injector could contain a full two- or ten-day course of gentamicin for a neonatal sepsis patient, with variable dose settings depending on the infant's weight. This approach could make it easier for a health care worker in a primary health setting to correctly dose and deliver gentamicin. Unlike other prefilled alternatives, a custom-designed pen injector could have the advantage of enabling use of the same gentamicin presentation to treat infants of various sizes, rather than requiring different prefilled devices for different weight bands. The cost of developing and manufacturing a complex device could, however, be prohibitive in a cost-sensitive setting. The retail price of an insulin pen injector is approximately US\$40 in the United States, and an Indian manufacturer sells disposable pen injectors filled with insulin for US\$3.50.⁵⁶

Figure 11. A) Insulin pen injector and B) Duoject's VaccJect device.



A



B

Photo: A) PATH and B) Duoject

3 Alternative formulations of gentamicin for different routes of delivery

Gentamicin is a polarized water-soluble compound with very poor intestinal permeability that results in low oral bioavailability. Because of poor absorption after oral administration, gentamicin is clinically used in parenteral or topical dosage forms. In the case of neonatal sepsis, gentamicin is only licensed for parenteral delivery, which allows for adequate bioavailable levels in blood to treat the bacteria responsible for sepsis. However, there is a need for exploring alternative routes of delivery for gentamicin. The administration of drugs by non-parenteral routes, such as transdermal or transmucosal routes, are needle-free and relatively painless, can be more acceptable to patients and parents, and may result in increased compliance. Alternative routes can also reduce the time a health worker would require

to deliver gentamicin, including time spent preparing an IM injection or establishing IV access. Safety can also be improved for the health care provider, patient, and community by eliminating sharps, and costs could be saved if additional delivery devices and sharps waste disposal are not required. These alternative methods also provide clinical care providers with more choices to better manage their patient's course of treatment.

We have reviewed various routes of delivery—oral, sublingual, intranasal, pulmonary, rectal, and transdermal—to assess whether any could be viable alternatives to IM injection for gentamicin. For each delivery route, we reviewed literature on research to date and summarized the feasibility of developing formulations, taking into consideration technical feasibility, cost, and programmatic suitability.

3.1 Oral

Technology description: For drugs that act systemically, providers often use the parenteral delivery method rather than an oral method due to its pharmacokinetic advantages, poor intestinal absorption of oral medicines, and the inability of patients to take medication by mouth. However, a literature review conducted by the WHO (utilizing studies from 1996 to 2000) indicated that for many antibiotics such as penicillin, fluoroquinolones, chloramphenicol, sulfonamides, and rifampin, there is minimal to no pharmacokinetic benefit of IM injection versus oral administration in neonates.⁵⁷ Therefore, investigating oral routes for delivery of gentamicin might prove to be a viable alternative to injections. Oral medicines can take liquid or solid form, and both dosage forms have several advantages and disadvantages. For example, both liquid and solid forms of oral medication eliminate the need for needle and syringe. The solid dosage form is advantageous due to its higher physiochemical stability and relative ease of transportation and storage, whereas the liquid dosage form is advantageous due to the ease of ingestion for neonates.

Chewable tablets, dispersible tablets, and orodispersible tablets are solid formulations often used for oral medication. Chewable tablets can be chewed prior to swallowing and do not require water, but they require dentition and therefore are suitable only for children aged > 6 years. Dispersible tablets are dispersed in water prior to ingestion to form a stable suspension. Disintegration times of dispersible tablets can be as low as 20 seconds, but potable water or milk is required for dissolution. As it is delivered as a liquid, this design is suitable for neonates. Orodispersible tablets are systems that do not require external liquids and disintegrate in saliva within 60 seconds, leaving an easy-to-swallow suspension in the mouth. This design is suitable for infants > 1 month.⁵⁸

Oral liquid preparations are ingestible formulations administered as solutions or dispersions. They are considered acceptable for children of any age and therefore could be a viable option for gentamicin administration in neonates. Oral suspensions containing amoxicillin have been explored in depth for infants and they are marketed under many trade names including Amoxil, Moxatag, and DisperMox. Starting as a powder, Amoxil can be reconstituted to form a fruit-flavored syrup containing sodium benzoate as a preservative. Oral liquid preparations require packaging with appropriate administration and

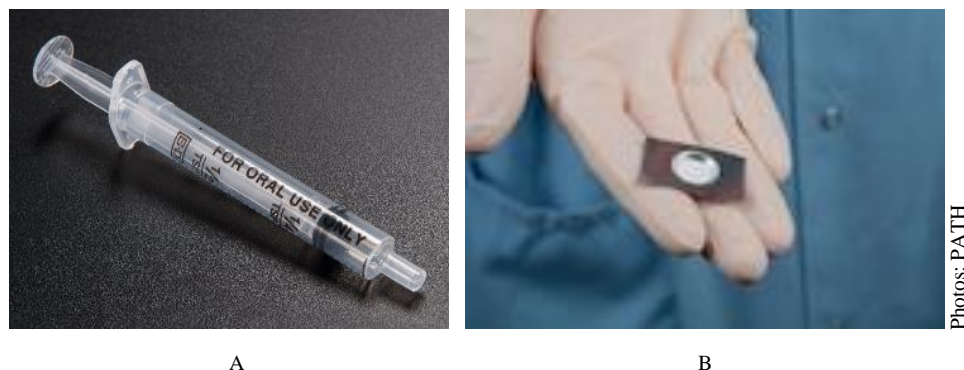
dosing devices, and due to their lower physiochemical stability, they may require refrigeration to ensure stability during transportation and storage. To overcome the storage constraint, liquids could be supplied as powders and reconstituted in potable water prior to administration. Other liquid forms starting as granules or pellets that can be dispersed in water could be formulated. However, studies of these formulations are scarce. Additionally, with these formulations, there is a risk of incorrect dosing during volume measurements. See Figure 12 for examples.

As a class of antibiotics, aminoglycosides, such as gentamicin, are poorly absorbed from the gastrointestinal tract and are commonly presented as injectables for systemic delivery and topical preparations for local drug delivery.⁵⁹ Oral formulations of gentamicin have been previously studied in the treatment of severe diarrhea in infants and in other bacterial infections of the gastrointestinal tract, including *Klebsiella pneumonia* infections.⁶⁰ Oral gentamicin dosages ranged from 50 to 80 mg/kg depending on the condition.⁶¹ Oral gentamicin for systemic drug delivery has also been explored. Preclinical studies in rats using Labrasol as an emulsifier have reported > 50% increase in bioavailability of gentamicin given orally, enhancing gentamicin absorption from the gastrointestinal tract into systemic circulation.⁶² Admixtures of gentamicin with a glycosteroid TC002 also reportedly increased the oral bioavailability of gentamicin in both rats and dogs, demonstrating the ability of glycosteroids as a drug transport agent for promoting intestinal absorption of polar molecules such as gentamicin.⁶³

Implications for expanding access: Although the ease and convenience of an oral gentamicin formulation could reduce the amount of training required by a health worker, this mode of delivery would require extensive research to develop a new oral formulation of gentamicin. The new oral formulation would need to address gentamicin's poor bioavailability by incorporating transport agents that could increase intestinal absorption. In addition, palatability for infants is necessary for successful drug intake and the gentamicin formulation would need to mask the bitterness of the antibiotic.

Costs associated with the oral route of gentamicin delivery are expected to be comparable or slightly lower than IM and IV routes, with liquid presentations having a slightly higher cost than solid presentations due to additional transportation and storage requirements. Liquid doses can be presented in multi-dose bottles for delivery with an oral syringe or in single dose containers, such as BFS ampoules, that are low cost compared to prefilled devices for IM injection. Solid doses can be transported as dispersible tablets that would reduce the costs of primary packaging, thereby lowering the cost of this dosage form. Ease of delivery and use are advantages of an oral gentamicin presentation if reformulation is successful.

Figure 12. Examples of technologies for oral delivery. A) Oral syringe and B) dispersible tablet to be dissolved in water.



3.2 Sublingual

Technology description: Sublingual delivery of medications utilizes the mucosal membranes lining the floor of the mouth to reach systemic circulation and avoid first-pass metabolism. Sublingual technologies can come in the form of tablets or films (Figure 13). The system has many advantages: it allows ease of administration to pediatric patients who cannot swallow tablets, it reduces errors of improper dosage compared to liquid formulations, and it does not require water for the swallowing or dissolution of the medication. Tablets, however, are solid and require patient compliance, and therefore can only be used in children > 6 years or capable of maintaining the tablet in the right place without swallowing saliva for 1 minute. Choking on the sublingual tablets is also a concern for pediatric patients. To date, pediatric sublingual tablets have been restricted to medicines to treat allergies in children > 5 years.⁵⁸

Thin films are another method of sublingual drug release. Like tablets, thin films dissolve in the mouth and reach systemic circulation through the mouth's mucosal membranes. The increased surface area of the thin film can allow it to dissolve more rapidly than tablets and some providers prefer this method because it eliminates the fear of choking, an especially important concern in infants.

If gentamicin were to be formulated into either sublingual tablets or thin films, a potential disadvantage to these formulations would be unintentional swallowing of the medicine. The sublingual route relies on the user's ability to hold the object in place under the tongue for approximately one minute without swallowing. Because providers cannot rely on neonates to display this level of control without swallowing, it is likely that inconsistent drug absorption would ensue, which may lead to unintended toxicity.

Implications for expanding access: With the exception of penicillin, an antibiotic that has long been researched as a candidate for sublingual delivery, minimal research has been conducted on sublingual antibiotics. Gentamicin-containing sublingual tablets or films have not yet been developed for adult or pediatric use. Thus, further research would be necessary to develop a sublingual formulation and to determine the feasibility of gentamicin sublingual delivery. As with the oral route, palatability would be

an important consideration for a sublingual gentamicin formulation. To treat neonatal sepsis, the sublingual tablets or films containing gentamicin must be dissolved externally and then delivered as a liquid. This would alleviate the possibility of choking, but it would not, however, eliminate the possibility of swallowing. An infant that accidentally swallows a sublingual dose would require another dose to ensure adequate antibiotic amounts were delivered. This could result in inconsistent absorption of the antibiotic and could potentially raise the serum concentrations of the drug to toxic levels. Due to these concerns, a sublingual formulation of gentamicin for neonatal sepsis is unlikely to be feasible for our target population.

Figure 13. Example of sublingual tablets.



3.3 Intranasal (spray or drops)

Technology description: Nasal delivery is a route for systemic drug delivery that would eliminate the need for an injection and circumvent issues related to slow absorption of the gastrointestinal tract that have been observed in oral gentamicin formulations. Nasal delivery can take the form of sprays, drops, and powder formulations. For each case, a delivery device is needed to accompany the dosage. Nasal dispensing systems for pediatric use are generally slimmer and the dosage volume is reduced. A limitation that has delayed clinical implementation of neonatal nasal sprays is the small volume that is allowed per nostril. Volumes of 0.2 to 0.3 ml per nostril are recommended for pediatric patients, but up to 1 ml can be tolerated.⁶⁴ Volumes for neonatal patients should be adjusted to reflect infant size, as nasal cavity size fluctuates widely among pediatric patients. Intranasal devices are available in mono-dose and bi-dose designs. Mono-dose devices are designed to deliver the entire dose to one nostril and bi-dose devices are designed to deliver half a dose to each nostril.

Nasal sprays are applied to the nasal cavity (targeting the mucosa) and multi-dose presentations traditionally contain preservatives to maintain microbiological stability. Some studies have shown that these preservatives can cause irritation and reduce ciliary movement.⁶⁵ Another disadvantage of this method is the spray's strong impact on nasal mucosa, which can also result in local irritation and additionally restricts the area for drug deposition.⁶⁵ Fill-on-site (non-prefilled) liquid spray devices can be single- or multi-use. Single-use devices generally consist of a standard syringe fitted with a nosepiece spray device and metered valve. Multi-use devices are typically designed as a pump spray that fits onto a vial. Prefilled devices come with the dose preloaded and often require fewer steps to operate. The reduced

number of steps can shorten the time required to deliver the dose and can reduce the potential for user error in the preparation process. See Figure 14 for examples of prefilled liquid spray devices.

Nasal drops, also applied to the nasal mucosa, are preferred for infants since one or two drops can cover the whole mucosa in the infants' nasal cavity. Although drops are usually supplied in multi-dose containers (along with a suitable dispensing device such as a dropper or syringe), inexpensive single-dose ampoules produced by BFS technique are possible nasal dropper systems. An advantage of single-dose systems compared to multi-dose systems is that preservatives are not required.⁶⁵ Other benefits of droppers are their relatively low cost and ready availability compared to other nasal delivery devices. However, it is important to position the patient correctly to ensure proper delivery of the dose and prevent the vaccine from running out of the nostrils. See Figure 15 for examples of liquid droppers that could be used for intranasal drops.

Another option for nasal delivery are powder formulations which stick to the surface of the nasal mucosa before dissolving. Moisture sensitivity, solubility, particle size and shape, and flow characteristics all affect powder absorption. Nasal powders offer greater stability than liquid formulations and may not require preservatives.⁶⁵ Many devices under development for intranasal delivery of powder formulations are active devices that use mechanically compressed air to expel the drug powder when activated. This is performed using a compressible compartment that provides pressure to create a plume of powder similar to the liquid droplet plume created by liquid spray devices. These devices are designed for a variety of functions and can be mono- or bi-dose and single-use or multi-use.

Implications for expanding access: Several studies have been conducted to determine the feasibility of gentamicin as microparticles or microspheres in a nasal delivery system. A 2002 study explored the nasal administration of gentamicin via an insufflator in rabbit models.⁶⁶ Gentamicin sprays were evaluated with and without microparticulate systems composed of two mucoadhesive polymers, hyaluronic acid (HA) and chitosan hydroglutamate (CH), and serum levels and bioavailability were measured in each condition. The HA/CH microparticles produced mean serum gentamicin concentration at 30 minutes (1.53 ± 0.35 µg/ml) and 60 minutes (1.29 ± 0.34 µg/ml), demonstrating the necessity of mucoadhesive polymers to increase the bioavailability of the antibiotic (> 30%) compared to simple nasal gentamicin solution. The serum concentrations demonstrated in the study were lower than the desired therapeutic gentamicin concentration with a target peak concentration 10.0 to 12.3 µg/ml, but it is possible that with a dose adjustment, a gentamicin-containing nasal delivery device could be developed for neonatal and pediatric use.⁶⁶

From a cost perspective, nasal droppers may be cheaper than nasal spray devices. Nasal droppers could be developed in prefilled single-dose presentations such as BFS, or in multi-dose presentations with a separate delivery device, such as a glass vial with an oral poliovirus vaccine dropper cap. The cost of a simple dropper device could be similar to IM injection, or slightly lower due to the lack of a needle and syringe. Nasal drops would also be advantageous if the delivery device and dosing regimen could be demonstrated to be simple enough for safe use by a health worker with minimal training.

Figure 14. Examples of prefilled liquid spray devices. A) BD Accuspray device used for MedImmune's FluMist® influenza vaccine, B) Mystic Pharmaceuticals ArrowFish, C) Nemera nasal pump spray system.

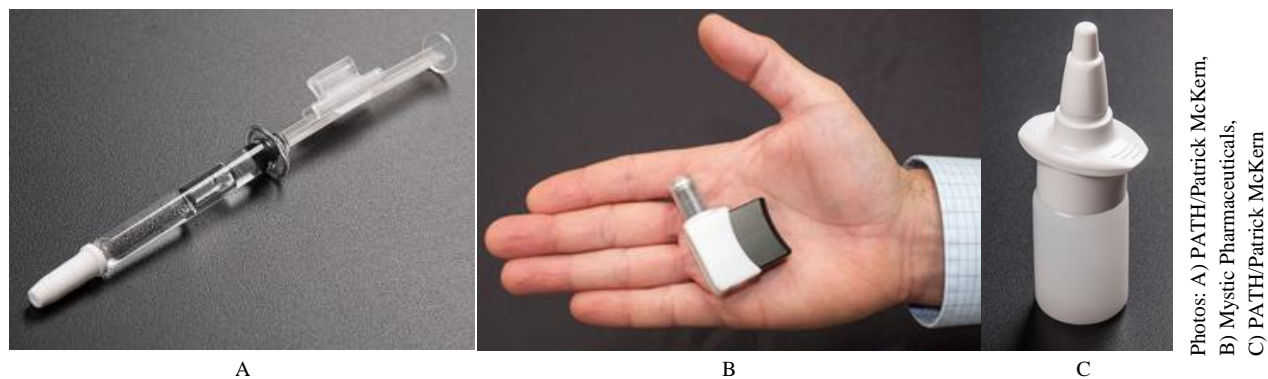
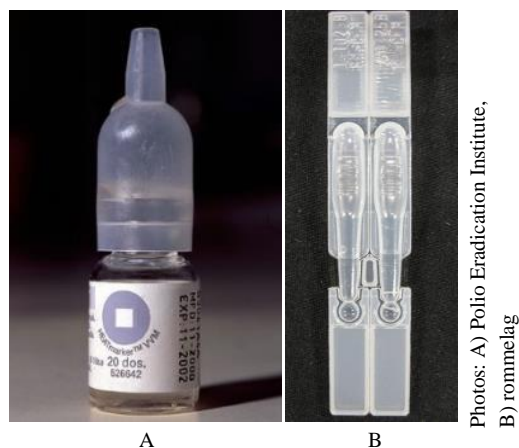


Figure 15. Examples of droppers that could be used for intranasal drops. A) Glass vial of oral poliovirus vaccine with a dropper device for oral delivery and B) rommelag BFS single-dose, intranasal liquid droppers.



3.4 Pulmonary (inhalation)

Technology description: Aerosol administration of therapeutics to the pulmonary epithelium for systemic delivery represents a significant opportunity for many classes of drugs and for both small molecules and macromolecules.⁶⁷ This method utilizes large alveolated regions of the lungs to provide effective drug absorption. In contrast to oral delivery, where a drug can be heavily metabolized and altered by the enzymes of the gastrointestinal tract and liver (hepatic first pass effect), the lungs have only a small fraction of the drug-metabolizing and efflux transporter activity of the gastrointestinal tract and liver.^{68,69,70} Thus, small molecules can be delivered very efficiently into the body through the lungs without the production of a complex array of metabolites. A number of companies are in advanced clinical trials with inhaled insulin,⁷¹ and a variety of large and small molecules are under investigation as inhaled formulations for systemic applications.

Lung deposition depends not only on properties of the drug, such as particle size and dose volume, but also on the amount of air inhaled. There are three types of aerosol devices: metered-dose inhalers (MDIs),

dry powder inhalers (DPIs), and nebulizers (a delivery device that uses oxygen or pressurized air to administer medication into aerosols that are then inhaled from a mouthpiece). MDIs contain liquid medication held in a pressurized canister that is delivered as an aerosol spray. A spacer (a device consisting of a small chamber placed between the aerosol generator and the patient's mouth) may be used with MDIs to improve delivery of the medication to the lungs. DPI design is similar, but these devices release a puff of dry powder rather than liquid. Nebulizers convert liquid medication into a mist that is then inhaled into the lungs. All three devices are equally efficient: 10% to 15% of the starting drug dose is delivered to the lungs. However, since a nebulizer dose is often 11 to 12 times larger than an MDI dose, more drug reaches the lung with the nebulizer, causing this system to be preferred by many clinicians.⁷² MDIs can reach the same clinical effect by increasing the number of puffs. See Figure 16 for examples of pulmonary delivery devices.

Inhaled antibiotics have long been used for the treatment of chronic respiratory infections. Tobramycin, colistin, and aztreonam are currently marketed for treatment of infections in cystic fibrosis patients and are available as nebulized liquids or dry powder for inhalation.⁷³ Other antibiotics have been used off-label for pulmonary delivery for treatment of conditions including ventilator-associated pneumonia and for lung transplant recipients.⁷³ A 2011 study evaluated the efficacy of nebulized gentamicin in treating non-cystic fibrosis bronchiectasis.⁷⁴ In this study, patients were treated twice daily with 80 mg nebulized gentamicin (injectable formulation diluted with saline), and it was determined that after a year of pulmonary treatment with the antibiotic, there was significantly reduced sputum bacterial density and airway inflammation. However, despite the significant bacterial clearance locally, there was little change in systemic inflammation after the year-long gentamicin treatment.⁷⁴

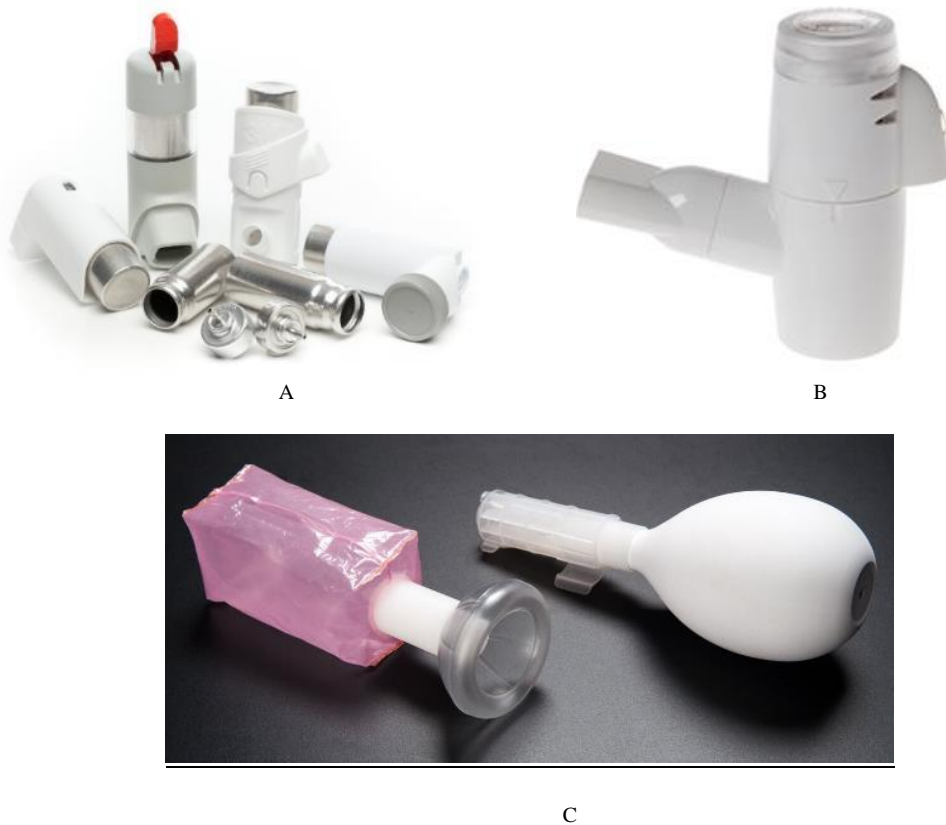
Gentamicin has also been studied as a direct respiratory system therapy to treat tuberculosis. The treatment of aerosolized gentamicin, administered at 5 mg/kg to mice five days per week for one month, was shown to significantly reduce the tuberculosis infection in the mouse model.⁷⁵ NanoGENT™ is a dry powder for inhalation, similarly developed to treat respiratory infections such as pneumonia and tularemia. NanoGENT™, delivered using the Respirics ACU-30™ dry powder inhaler (DPI) inhaler, contains 80% gentamicin sulfate with each 25-mg dose delivering 10 to 15 mg gentamicin sulfate to the respiratory tract. Studies have shown that the device produces higher local drug levels in the lungs than the IV route.^{76,77}

Implications for expanding access: Studies have demonstrated gentamicin's potential efficacy in localized respiratory infections. However, cellular uptake of the drug is a limitation for systemic activity. A veterinary study examined the cellular uptake of gentamicin when encapsulated by liposomes and concluded that liposomal gentamicin was tolerated in foals and resulted in higher intracellular drug concentrations than free gentamicin.⁷⁸ For an inhaled gentamicin route to be feasible for sepsis treatment, reformulation activities would be necessary to ensure drug absorption from the lungs into systemic circulation, potentially using liposomes or another carrier system.

Inhalers are a less invasive drug delivery route and can eliminate errors associated with improper dosing if a single-dose, prefilled device is used. However, unlike nasal sprays, transport of the aerosol into the

lungs depends on active inhalation by the participant, which is not feasible for neonates or children under 5 years. It is possible that utilizing a pressurized inhaler could circumvent this issue; when combined with a spacer system, these types of inhalers can be used by infants. However, this adaption is likely to add to the cost of the system, making it perhaps less feasible for gentamicin delivery in low-resource settings. Nebulizers are also suitable for infant use, but they would still impose a burden on the health worker who would need to prepare the device and administer it. It would require diligent cleaning of the specific nebulizer or tubing supplies, and it would require compressed air and a power source in a facility that might not have these resources. Nebulizers are also relatively expensive, reusable devices and could be costly for primary care centers that see few sepsis cases.

Figure 16. Examples of pulmonary devices. A) Metered dose inhaler from 3M, B) Aeroneb® Go liquid aerosol nebulizer by Aerogen, and C) PuffHaler dry powder inhaler used in clinical testing for delivery of powdered measles vaccine to adults.



Photos: A) 3M, B) Aerogen, and C) PATH/Patrick McKern

3.5 Rectal

Technology description: The rectal route is an alternative delivery method that allows both local and systemic drug release and is a possible candidate for gentamicin delivery in neonates. Suppositories are a common dosage form for rectal drug administration; they are inserted into the rectum where they dissolve or melt and are then absorbed systemically. Other rectal forms include creams, ointments, gels, foams, gelatin capsules, and small-volume solutions (Figure 17). Generally, the rectal dose needs to be higher than the dose administered by the oral, intravenous, or intramuscular routes.⁷⁹ Administration can be performed by caregivers or health workers with minimal training. This is an advantageous feature in low-resource settings where frequent hospital access is not possible. Rectal administration has many potential advantages including: enhanced drug absorption, partial avoidance of hepatic first pass (depending on area of drug administration in the rectum; drugs administered in the lower part of the rectum can bypass the liver, resulting in the avoidance of hepatic first pass metabolism and producing systemic circulation), retention of large volumes, and rate-controlled drug delivery. Conversely, there are several disadvantages to this delivery method as well: erratic absorption of drugs across the rectal mucosa, limited absorption surface area and fluid availability for drug dissolution, and premature expulsion of the drug. To overcome these challenges of absorption, several adjuvants such as amino acid enamines, salicylates, and fatty acids have been studied.⁸⁰ Another difficulty for the development of a neonatal rectal suppository is the lack of studies involving infants. Rectal forms are often only available in doses suitable for adults and older pediatric patients and rectal drug absorption in newborns can be variable.⁸¹ Therefore, if this route is to be pursued for neonates, it must be evaluated carefully for safety, efficacy, and appropriate bioavailability. Cultural acceptability and parent compliance might be another limitation of the rectal route of antibiotic delivery.⁸¹ Studies concerning user compliance and acceptability would be necessary to assess the feasibility of a rectal suppository.

Implications for expanding access: Rectal drug uptake has been studied extensively for drugs like diazepam, acetaminophen, indomethacin, methadone, and diflunisal, which have all been approved for market use.⁸² Several studies on rectal delivery of gentamicin have been conducted in recent years in animal models, demonstrating absorption enhancement using various adjuvants. One such study examined the enhancing effect of salicylates on rectal absorption in rabbits and found that coadministration of gentamicin along with the salicylates was more effective in powdered form rather than solution form, suggesting that suppository form should be considered further in gentamicin research.⁸³ Other studies have examined the enhanced rectal absorption of gentamicin formulations using fatty acids (sodium octanoate, sodium hexanoate, and glycerol-1-monooctanoate) and phenothiazines as formulation adjuvants.^{84,85} Absorption results from these studies have been promising and point toward the rectal route as a candidate for gentamicin delivery. However, more research is needed on gentamicin delivery via the rectal route in humans, and more specifically in neonates. An antibiotic-containing suppository to treat sepsis as a low-cost and safe alternative to the injectable format is currently under development by researchers at the University of Oxford.⁸⁶

One possible limitation of this delivery route is the cultural acceptability of rectal drug administration. It is possible that health care worker or parent discomfort with this route might hinder its implementation. Another challenge for this route of delivery is its physical stability during transportation and storage. Suppositories are designed to melt at body temperatures, a property that allows fast absorption via rectal mucosa, so they would require controlled temperature storage. Cost is likely to be an advantage of this delivery route; the price of a rectal suppository or gel would potentially be comparable to that of an oral tablet or liquid.

Figure 17. Examples of over-the-counter rectal suppositories. Laxative glycerin suppositories for children (left) and FeverAll® acetaminophen suppositories for infants (right).



3.6 Transdermal

3.6.1 Transdermal patches

Technology description: Transdermal patches are commercially available for multiple pharmaceuticals, including contraception, nicotine replacement therapy, and pain medications. Transdermal patches adhere to the skin and the pharmaceuticals they contain passively diffuse into circulation. Transdermal delivery is a noninvasive method of administering potent, lipophilic compounds with sustained release rates. It provides release for short or long periods of time (up to 1 week).⁶² Following a diagnosis of sepsis, a health worker could potentially apply a long-acting patch to continuously provide therapeutic levels of drug over the number of days required for treatment. Alternatively, if patch re-application at intervals is necessary, a health worker or potentially a parent could be trained to apply subsequent doses.

Implications for expanding access: For effective delivery through the skin barrier, drugs must be lipophilic, small molecules. This has limited the applicability of transdermal patches to a relatively small number of drugs. Gentamicin is a water-soluble drug and therefore cannot be delivered across intact skin using conventional transdermal patches. However, the recently developed hydrogel microneedle patch is a novel technology that addresses this barrier (see section 3.6.2 below). Additionally, few transdermal

patches are intended for pediatric patients because the skin's permeability fluctuates widely from birth to adulthood; infants have a much larger surface-area-to-weight ratio than adults, increasing the percutaneous absorption and the systemic effects of the drug.

3.6.2 Hydrogel microneedle patches

Technology description: Microneedle patches consisting of an array of solid coated or dissolvable micron-scale projections have been extensively investigated for delivery of vaccines and potent therapeutics, such as insulin, where only a small dose is required for a physiological response.^{87,88} The relatively high doses required for gentamicin (10 to 17.5 mg for neonates) preclude the use of conventional microneedles. However, an innovative microneedle technology developed by Queen's University Belfast can enable transdermal delivery of many high-dose, low-molecular-weight drugs that are not feasible to deliver transdermally by other methods.⁸⁹ Hydrogel microneedle patches are made from a biocompatible cross-linked polymer system that is hard in the dry state. Upon skin application, the microneedles rapidly swell to form a continuous, aqueous pathway between the rich dermal microcirculation and an attached lyophilized drug reservoir (Figure 18).⁹⁰ Skin interstitial fluid is drawn by osmosis through the swelling microneedles toward the porous, hygroscopic drug reservoir, which is encased in a protective water-impermeable backing layer to protect it from atmospheric moisture. Upon rapid dissolution in the absorbed fluid, the rate of drug delivery into skin is controlled by modulation of the crosslink density of the hydrogel matrix. The microneedles are removed intact, depositing no polymer in skin and are too soft for reinsertion, thus eliminating the need for sharps disposal. Based on preclinical studies, it is estimated that this patch technology could deliver 1,200 mg a day of the model drug ibuprofen to adults. Therefore, designing a patch that is suitable for gentamicin delivery to infants based on this technology is feasible.

The United Nations Commission for Lifesaving Commodities for Women and Children identified a gentamicin microneedle patch as a possible product innovation.⁹¹ A hydrogel microneedle system would have numerous advantages over delivery of gentamicin using standard needles and syringes, including ease of use, potential for administration by less-experienced personnel, reduced dose-calculation errors, increased acceptability by caregivers, and avoidance of transmission of blood-borne infections through needlestick injuries. The patches are designed to be easy to apply and have been shown to facilitate consistent, reproducible self-application by non-medically trained volunteers.⁹² Microneedle patches for vaccine applications have been advanced for use in low-resource settings due to the potential low cost, ease of use, safety, and stability of the technology; enabling delivery of vaccines such as inactivated polio vaccine and measles house to house by campaign volunteers would be particularly useful in eradication efforts.^{93,94,95,96} Modeling has demonstrated the potential cost-effectiveness of influenza vaccine microneedle patches if they can increase coverage and reduce administration costs.⁹⁷ Microneedle patches have been found to be pain free and acceptable to patients, including delivery by self-administration in adults.^{92,98} Further research will be required to assess acceptability of gentamicin patches to infants, caregivers, and health care workers. Hydrogel microneedle patches are currently at a very early stage of development. PATH has recently initiated a project working with Queen's University Belfast to apply this technology to gentamicin and assess the feasibility of this route of delivery. Development of this

technology will entail incorporating gentamicin into a polymer formulation that has the required mechanical properties of a hydrogel microneedle patch.

Figure 18. Hydrogel microneedle patch and close-up of microneedle projections.

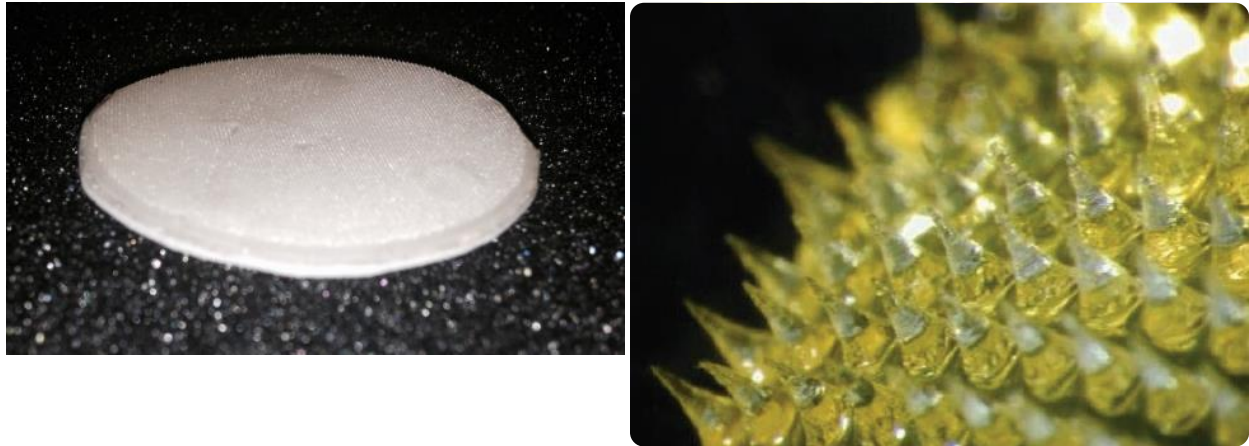


Photo: Ryan Donnelly/Queen's University Belfast

4 Summary and recommendations

4.1 Summary

This review identified several factors that would influence the selection of alternative formulation, packaging, and delivery technologies for gentamicin for outpatient treatment of neonatal sepsis. In general, packaging and delivery devices for IM injection of gentamicin would be a shorter term solution to address the needs of health workers and patients given that the platforms utilize a commercially available formulation of gentamicin and there is extensive clinical data for this route of delivery for treatment of sepsis. Alternative formulations of gentamicin for different routes of delivery would be longer-term solutions, given that such formulations are not commercially available, and preclinical and clinical data would be required to demonstrate the efficacy of a novel route of delivery. However, some alternative routes of delivery have significant potential benefits in acceptability and ease of delivery, which could be worthy of further development.

The main factors that should be considered in determining which technologies should be advanced for neonatal sepsis treatment include technical feasibility, usability, sharps safety, cost, pharmaceutical manufacturer considerations, and compatibility with health system logistics.

4.1.1 Technical feasibility/timeline

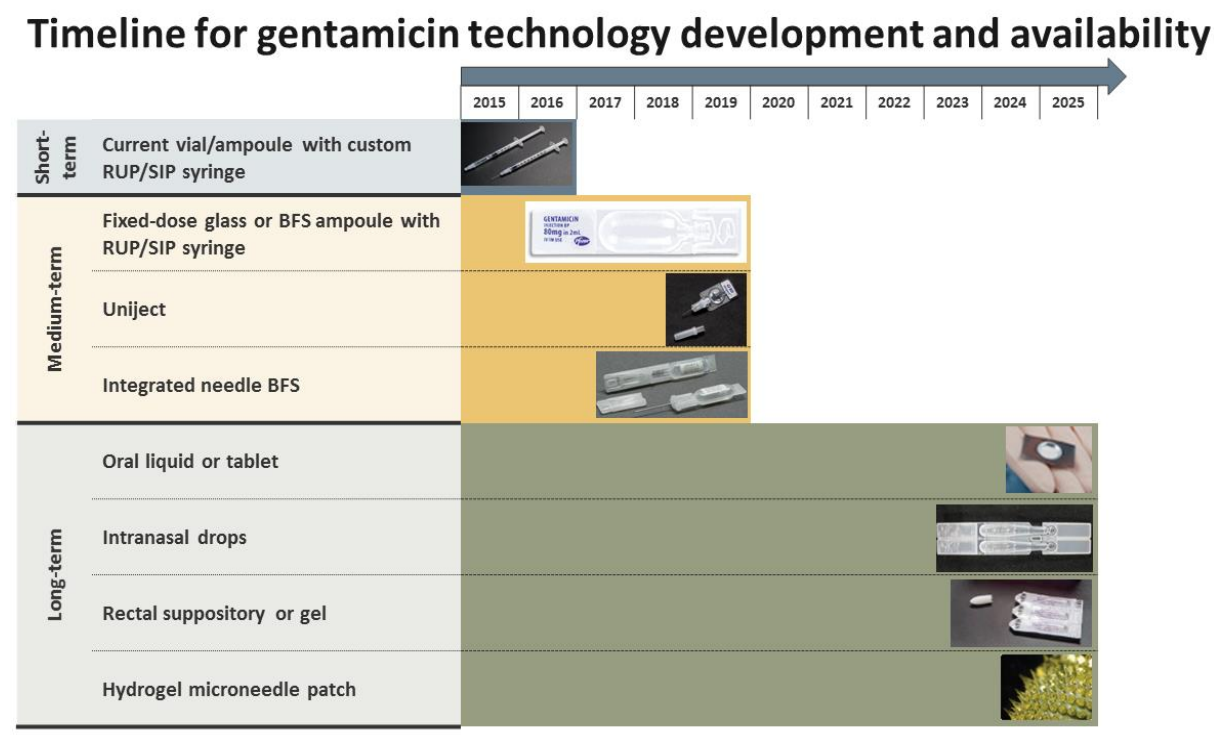
4.1.1.1 Packaging and delivery devices for intramuscular injection of gentamicin

Some alternative IM delivery devices, such as custom-printed syringes, could be rapidly implemented as they would not require a change to current gentamicin manufacturing and fill/finish processes (see Figure 19). Alternative dose presentations in new primary containers, such as fixed-dose BFS ampoules and prefilled IM delivery devices such as Uniject, would require a mid-range timeline to implement due to regulatory processes. However, as evidenced by currently marketed gentamicin products in non-glass containers (such as Pfizer's gentamicin in BFS ampoules), gentamicin is compatible with polymer materials so this approach is likely to be technically feasible.

4.1.1.2 Alternative formulations of gentamicin for different routes of delivery

Gentamicin is currently delivered IV or by IM injection to obtain the systemic drug concentrations necessary to treat the bacterial infections causing sepsis. While some alternative delivery routes, such as oral delivery, might be optimal from a user's standpoint, formulation and pharmacologic challenges have prevented use of these routes for gentamicin to date. It is possible that with reformulation, and preclinical and clinical testing, an oral gentamicin presentation could be developed. However, this would require a long-range timeline. Other alternative routes, such as sublingual delivery formulations and hydrogel microneedle patches for the delivery of gentamicin have not yet been developed and would also require reformulation. Preliminary formulation research has been conducted for the intranasal, pulmonary, and rectal routes of gentamicin delivery. Extensive preclinical and clinical studies would also be required for all new routes of delivery to establish the correct dosing, compare efficacy to the IM route of delivery, and confirm safety, as well as to support regulatory approvals.

Figure 19. Timeline for gentamicin technology development and availability.



Acronyms: BFS, blow-fill-seal; RUP, reuse prevention; SIP, sharps-injury prevention.

4.1.2 Usability

4.1.2.1 Packaging and delivery devices for intramuscular injection of gentamicin

The target providers of outpatient treatment with gentamicin include trained health care providers at the primary care level. Each device reviewed offers some type of simplification of the delivery method, which would alleviate many problems associated with improper dosage or administration and could make it easier, faster, and safer for health care workers in a primary care setting to provide the correct dose of gentamicin to newborns with symptoms of sepsis. However, the steps that are simplified and the degree to which the function of the devices resemble a needle and syringe differ. Determination of an appropriate technology depends on the capabilities and program authorization of the intended user groups in specific countries. If safe and easy-to-use presentations and delivery devices were available, gentamicin delivery might also be expanded to include those with lesser training, such as community health workers, or possibly even parents themselves. In many settings, community health workers are not trained or permitted to use a standard needle and syringe to deliver injections. This is often related to a concern that providing training would encourage or enable them to become “injectionists” in the informal sector. Prefilled injection devices could alleviate these concerns and further expand settings for gentamicin treatment in countries that choose to evaluate this option.

4.1.2.2 Alternative formulations of gentamicin for different routes of delivery

An oral dose form might be optimal from a user's standpoint as it would eliminate the need for hazardous sharps and could be administered by health care providers, community health workers, or parents. However, an easy-to-swallow formulation (a liquid dosage form or dissolvable tablet) would be necessary for neonatal patients. Although the sublingual delivery route is attractive for the aforementioned reasons—it is pain free and eliminates the need for sharps—it is less feasible for neonates due to the potential for choking and unintended swallowing. Nasal droppers and hydrogel microneedle patches would be user-friendly and pain-free options for gentamicin delivery. Rectal delivery would be another needle-free method of delivering gentamicin to infants, but it is possible that cultural acceptability and user compliance with this delivery route might hinder its implementation. The usability and acceptability by health care workers and parents should be evaluated for any novel delivery route during the development process.

If packaged in a multi-dose format, the packaging and delivery device should be designed to facilitate delivery of the correct dose and route. Liquid formulations for oral, intranasal, and pulmonary delivery could also be developed in single-dose containers, which could increase cost but reduce the dangers associated with improper dosage. Solid dose forms such as dispersible tablets and rectal suppositories could also be easier to correctly dose than current IM presentations if a small number of weight bands could be used.

4.1.3 Sharps safety

4.1.3.1 Packaging and delivery devices for intramuscular injection of gentamicin

To improve the safety of patients, health care workers, and the community, use of technologies with reuse-prevention and needlestick-prevention features is recommended and would be particularly important in settings where safe sharps-disposal practices may not be properly observed.

4.1.3.2 Alternative formulations of gentamicin for different routes of delivery

Alternative routes of delivery have the potential to eliminate needles and the risk of sharps injury. Packaging and delivery devices for alternative routes should be developed to minimize the risk of accidental injection of formulations not intended for parenteral delivery. For example, oral syringes (which are not compatible with luer needles) could be provided for oral liquid formulations in a multi-dose bottle presentation.

4.1.4 Cost

4.1.4.1 Packaging and delivery devices for intramuscular injection of gentamicin

Each alternative packaging and delivery approach described offers a benefit in terms of dose accuracy, safety, or ease of use, but will likely require some added cost over the currently available product. The setting for this application is known to be price sensitive. The most affordable solutions are likely to be

reuse-prevention needles and syringes with single-dose medication ampoules. Prefilled technologies would offer greater benefits in ease of use, but even relatively low-cost prefilled options would generally be more expensive to implement than existing presentations of gentamicin.

4.1.4.2 Alternative formulations of gentamicin for different routes of delivery

Alternative routes that utilize simple, existing delivery technologies, such as oral syringes and nasal droppers, could potentially have comparable costs as existing presentations. The routes that require complex, reusable delivery devices, such as nebulizers for pulmonary inhalation, would likely have higher costs and would therefore be less feasible in a primary health care setting. Transdermal hydrogel microneedle patches are a novel technology and the costs of manufacturing are not yet known.

4.1.5 Factors affecting drug manufacturers

4.1.5.1 Packaging and delivery devices for intramuscular injection of gentamicin

Any of the prefilled or fixed-dose presentations of gentamicin would require the cooperation of a drug manufacturer to repackage and relabel their product and would be subject to the review requirements of a regulatory authority. Changing to a prefilled format would likely entail a more complex regulatory pathway than a fixed-dose vial or ampoule. In addition, changing packaging formats (prefilled syringes or cartridges, Uniject, and BFS ampoules) would necessitate purchase and installation of new filling line equipment, if the drug manufacturer did not already have this capability, or outsourcing of device filling to a contract manufacturer. Gentamicin must be filled using filling equipment dedicated to antibiotic products and cannot be filled with filling equipment used for other classes of pharmaceuticals. These steps would increase the start-up costs and complexity for packaging other than conventional vials and ampoules.

4.1.5.2 Alternative formulations of gentamicin for different routes of delivery

Development of a novel route of delivery for gentamicin would require significant investment in formulation development, preclinical and clinical testing, and regulatory submissions for the new product. Different packaging and filling equipment would also likely be needed, depending on the dosage form.

4.1.6 Logistics

4.1.6.1 Packaging and delivery devices for intramuscular injection of gentamicin

Stability of injectable gentamicin in the various primary containers described in this report is anticipated to be similar to glass vial presentations, though studies will be necessary to validate stability. Secondary packaging, such as a foil pouch, is required for some polymer containers to prevent gas and water vapor transmission. Glass containers and devices, such as glass prefilled syringes, are more prone to breakage during transportation. Unlike glass vials and ampoules, the polymer materials used for the plastic primary containers described in this report can also be safely disposed of by incineration at the clinic level. Reusable devices, such as DSJIs, could be more logistically challenging to distribute and store at each of

the primary health care facilities that could treat neonatal sepsis cases. WHO prequalification requirements for DSJIs include specifications for stability at the range of environmental conditions that can occur in a clinic or outreach setting, including temperature, humidity levels, and dust/water exposure.⁹⁹ Devices should not rely on external power sources, such as electricity or compressed gas.

4.1.6.2 *Alternative formulations of gentamicin for different routes of delivery*

Gentamicin for injection is stable stored at 2°C to 30°C, but storage constraints may differ for different formulations. Often, solid dose formats of antibiotics will maintain stability in higher temperatures over a longer duration than liquid dose formats; an exception is rectal suppositories, which can melt at high temperatures. Preservatives will be necessary for multi-dose presentations of liquid formulations. Nebulizer devices that require power sources and routine maintenance would be less suitable for use in a primary care setting.

4.2 Technology comparison

A high-level comparative evaluation was conducted to summarize the characteristics of the identified formulation, packaging, and delivery device technologies for use with gentamicin (Figure 20). Each technology was rated qualitatively according to the criteria described above (technical feasibility, usability, safety, cost, drug manufacturer requirements, and program logistics impact) as outlined in Table 6 and Table 7. All formulation, packaging, and delivery devices were included in the comparative evaluation with the exception of sublingual formats, which were reviewed in the landscape but found to be inappropriate for delivery to neonates.

Table 6: Criteria used to compare technologies for delivering gentamicin for treatment of neonatal sepsis.

Technical feasibility	Feasibility was ranked based on whether a technology would be expected to have a short-, medium-, or long-term timeline for product development and availability.
Usability	Measuring the required amount of drug based on the patient's weight and filling the delivery device with the correct dose is likely to be the most challenging step for the user and critical to the safety and efficacy of the intervention. The options were ranked based on the ease of filling with the appropriate dose and delivery to the patient, with prefilled delivery devices identified as the most user-friendly category.
Sharps safety	Safety of the patient, the health care worker, and the community are of critical importance. Delivery devices were rated on sharps safety factors, including whether the device incorporates reuse prevention features and needlestick-prevention features. Delivery technologies and formulations that do not use sharps for delivery were ranked highest.

Potential cost per dose	The intended markets for this application are cost sensitive, so the cost of drug packaging and delivery devices will be important to enable adoption. Since gentamicin is an inexpensive drug, the cost comparison focuses on the estimated incremental cost of goods sold (COGS) of a new formulation, packaging format, and delivery device.
Factors affecting drug manufacturers	The formulation, packaging, and delivery alternatives would require different amounts of investment and regulatory processes. Technologies were ranked based on the degree of involvement necessary on the part of drug and device manufacturers.
Logistics	Gentamicin presentations were assessed based on their anticipated storage and stability requirements.

Table 7. Scoring system used to evaluate gentamicin-delivery technologies against key criteria.

	Red (less desirable)	Yellow	Green (desirable)
Technical feasibility	Long-term timeline: technical feasibility not yet demonstrated; formulation and/or device development needed	Medium-term timeline: technical feasibility demonstrated or likely and/or repackaging required	Short-term timeline: no repackaging needed, technology could be rapidly applied
Usability	Requires measurement of dose	Device filled from fixed-dose presentation or with fixed-dose device, or dose-setting required on multi-dose device	Prefilled single doses
Sharps safety	Sharps with reuse-prevention features	Sharps with needlestick prevention features	No needles
Potential cost per dose	Cost of goods sold (COGS) estimate > US\$1.00	COGS estimate > US\$0.20 to ≤ US\$1.00	COGS estimate ≤ US\$0.20
Factors affecting drug manufacturers	Significant investment required (new formulation and manufacturing process)	Moderate investment required (new filling equipment, regulatory approvals needed)	Technology adoption could be independent of drug manufacturer

	Red (less desirable)	Yellow	Green (desirable)
Logistics	Potential for less stability than current injectable gentamicin presentation, and/or storage and maintenance of reusable device components required	Likely similar stability and storage requirements as current injectable gentamicin presentation	Potential for greater stability than current injectable gentamicin presentation

Figure 20. Comparison of current and potential gentamicin delivery technologies by key criteria.

Technology Type	Delivery Alternative	Technical Feasibility	Usability	Safety	Potential Cost per Dose	Drug Manufacturer Requirements	Logistics
Packaging and delivery devices for intramuscular injection of gentamicin							
Fill-on-site: Current presentation with separate delivery device	Current vial/ampoule with custom RUP syringe	●	●	●	●	●	●
	Current vial/ampoule with custom SIP syringe	●	●	●	●	●	●
	Current vial with DSJI	●	●	●	●	●	●
Fill-on-site: Fixed-dose presentation with separate delivery device	Fixed-dose glass ampoule with RUP syringe	●	●	●	●	●	●
	Fixed-dose glass ampoule with SIP syringe	●	●	●	●	●	●
	Fixed-dose blow-fill-seal ampoule with RUP syringe	●	●	●	●	●	●
	Fixed-dose blow-fill-seal ampoule with SIP syringe	●	●	●	●	●	●
	Fixed-dose vials with DSJI	●	●	●	●	●	●
Prefilled injection devices	Glass/polymer prefilled syringe	●	●	●	●	●	●
	Uniject	●	●	●	●	●	●
	Integrated needle blow-fill-seal	●	●	●	●	●	●
	Prefilled DSJI	●	●	●	●	●	●
	Autoinjector	●	●	●	●	●	●
	Pen injector	●	●	●	●	●	●
Alternative formulations of gentamicin for different routes of delivery							
Alternative routes of delivery	Oral liquid formulation	●	●	●	●	●	●
	Oral tablet formulation	●	●	●	●	●	●
	Intranasal drops	●	●	●	●	●	●
	Pulmonary inhaler or nebulizer	●	●	●	●	●	●
	Rectal suppository or gel	●	●	●	●	●	●
	Transdermal hydrogel microneedle patch	●	●	●	●	●	●

Acronyms: DSJI, disposable-syringe jet injector; RUP, reuse prevention; SIP, sharps-injury prevention.

4.3 Recommendations

A less-invasive, easy-to-use form of gentamicin could increase access to treatment for the approximately 10% of infants who show symptoms of possible serious bacterial infection during the neonatal period.¹⁰⁰ Novel formulations, packaging, and delivery devices could also benefit health workers and the health system by saving time, improving safety, and reducing the potential for delivery errors. Based on this landscape analysis, there are several approaches to gentamicin that are promising in the short-term and long-term to simplify delivery and expand access to treatment.

The least-disruptive and shortest-term option would be to distribute custom-marked syringes for use with existing gentamicin products (see Figure 19). The benefits of this approach to increase usability and correct dosing could be addressed through user evaluations in the field. In the medium-term, promising packaging and delivery options for IM delivery of gentamicin include fixed-dose presentations (such as glass or BFS ampoules) distributed along with separate syringes with reuse prevention and/or needlestick-prevention features. This approach is expected to be lower in cost and less complex for manufacturers and would be simpler to administer than currently available drug formats. Other leading medium-term options include compact, prefilled auto-disable delivery devices (which can cost less than traditional glass prefilled syringes), such as the Uniject or integrated-needle BFS devices. These would be easier for health care workers to use than technologies that have to be filled by the user at the point of use. Additionally, this approach would avoid the training requirements for health workers to give standard syringe and needle injections. The expected cost of these options may be a barrier.

For long-term development, promising alternative formulations of gentamicin for different routes of delivery include oral liquids or dispersible tablets, intranasal drops, a rectal suppository or gel, and transdermal hydrogel microneedle patches. These novel formulations are worthy of investigation, as they could significantly improve the acceptability, safety, and ease of delivery of gentamicin in outpatient settings. Formative technical feasibility research should be pursued for these novel formulation options.

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